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INVITAE

Join the ParaGANGlioma - More Support for *FH* in Hereditary Pheochromocytoma-Paraganglioma

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BACKGROUND

- The fumarate hydratase (*FH*) gene encodes the FH protein, which is a catalytic component of the Krebs cycle and is involved in tumor suppression.
- Heterozygous pathogenic or likely pathogenic variants (PV or LPV) in the *FH* gene have been shown to cause hereditary leiomyomatosis and renal cell cancer (HLRCC).
- There have been reports that individuals with *FH* PVs are also at risk for pheochromocytoma (PHEO) and/or paraganglioma (PGL), but evidence is limited and this association is thought to be rare with an incidence of 1% among *FH* PV carriers, if not refutable.
- Here we describe ten individuals with the *FH* LPV p.T234A identified via multi-gene panel testing (MGPT) at two diagnostic laboratories, all of whom have a personal and/or family history of PHEO.

RESULTS

- Eight individuals presented with PHEO as their sole lesion in the HLRCC spectrum (80%), one individual presented with synchronous PHEO, PGL, and papillary RCC (10%), and one individual was not affected with any HLRCC tumors but had a family history of PHEO and RCC (10%).
- Individuals with PCC were diagnosed between the ages of 28-68y and the majority (77.8%) had only one PGL tumor.
- The individual with the synchronous component tumors underwent somatic sequencing of his RCC and PGL, which demonstrated discordant results by tumor type. The papillary RCC revealed a heterozygous allelic frequency of the germline *FH* LPV, p.T234A (47% of 304 reads) without loss of the wild-type FH allele. The PGL demonstrated an allelic frequency of the p.T234A LPV of 84% of 359 reads with single copy deletion of the wild-type allele owing to 1q43 loss.
- Based on structural analysis, the threonine residue at codon 234 sits at the interface of two monomer subunits and this substitution is anticipated to result in a significant decrease in structural stability.
- This amino acid position is highly conserved and is predicted to be benign and deleterious by PolyPhen and SIFT *in silico* analyses, respectively.
- The allele frequency of p.T234A in the general population is 0.001% (3 of 251274 alleles).

ACKNOWLEDGEMENTS

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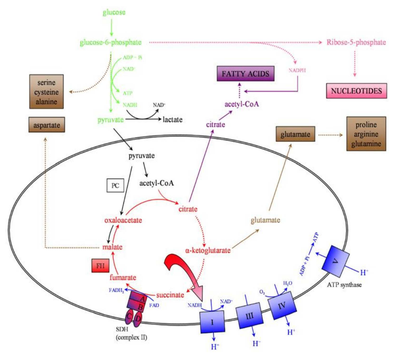
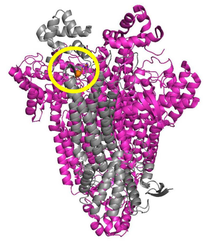
REFERENCES

- Castro-Vega LJ et al. *Hum. Mol. Genet.* 2014 May;23(9):2440-6.
- Richter S et al. *Genet Med.* 2019 Mar;21(3):705-717.

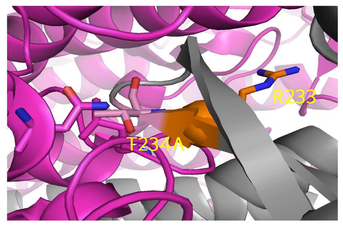
Pathway and Modeling



a. FH is a catalytic component in the Krebs cycle and interacts with complex II



b. Crystal structure of FH protein

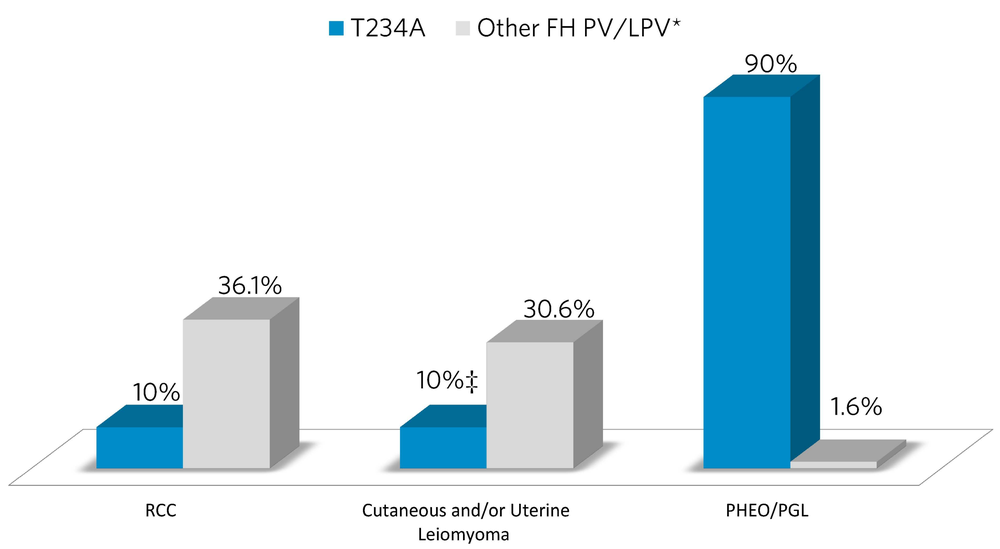


c. Threonine residue at position 234 is situated at the interface of two monomer subunits

Clinical Presentation of T234A Carriers

Pt #	Personal Cancer History	Family Cancer History
1	PHEO dx 50s, thyroid ca dx NOS	**Maternal**: PHEO, Breast, Ovarian; **Paternal**: Breast
2	Bilateral PHEO dx NOS, thyroid ca dx 70s	**Maternal**: Breast, Stomach; **Paternal**: CRC
3	Breast dx 40s	**Maternal**: CNS; **Paternal**: PHEO, RCC, Thyroid, Parathyroid, Pancreatic; **Other**: Thyroid
4	PHEO dx 40s, uterine leiomyomas dx 50s	None
5	PHEO dx 20s	**Maternal**: Uterine; **Paternal**: Ovarian
6	Lymphoma dx 50s, PHEO dx 60s	**Other**: PHEO, mesothelioma
7	PHEO dx 40s	**Maternal**: CRC, Pancreatic
8	PHEO dx 30s	**Other**: Ovarian
9	PHEO dx 50s	**Maternal**: Lung
10	PHEO dx 50s, PGL dx 50s, RCC dx 50s	**Maternal**: Leukemia; **Paternal**: RCC

Tumor Distribution in T234A Probands Compared to Other *FH* PVs and LPVs

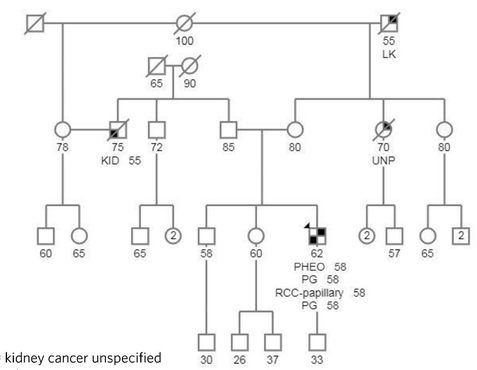


*Ambry MGPT probands with PVs and LPVs in *FH* through 2017, total = 62
‡Reflects updated clinical information since abstract submission

METHODS

- From January 2013 through September 2018, 27748 individuals had MGPT orders including the *FH* gene at Ambry Genetics, and of these, 7 were identified with the *FH* p.T234A LPV.
- Clinical history information for these 7 individuals was obtained via test requisition forms, clinic notes, and client communications.
- Clinical data for 3 additional p.T234A cases were ascertained through collaboration with another diagnostic commercial laboratory.
- The frequency of the p.T234A LPV in the general population was obtained from the Genome Aggregation Database (gnomAD).
- A known x-ray crystal structure of FH (PDB id: 5UPP) was used to analyze the structural effects induced by the variation.

Pedigree of Pt #10



KID = kidney cancer unspecified
LK = leukemia
PG = paraganglioma
RCC = renal cell carcinoma
UNP = unknown primary

TAKE-HOME POINTS

- Our results support a rare subtype of HLRCC in which PHEO is the predominant finding.
- While the extent of this disease subtype and penetrance in affected families is not yet known, we provide compelling evidence that the p.T234A variant is associated with PHEO/PGL development.
- These data illustrate the role MGPT plays in expanding the phenotypes of known syndromes.
- Collaboration between laboratories increased the significance of the clinical findings, provided independent validation, and aided in accurate variant classification.
- A better understanding of mechanism and genotype-phenotype correlation is needed to guide management, such as the need for specialized concurrent renal and adrenal imaging, and potentially the treatment of these tumors.